Pharmacy and Therapeutics Committee
Monograph

Testosterone Replacement Agents
Created 2/3/2012

Summary information provided. Consult package insert information for full prescribing information.

Conflict of Interest Information

This monograph contains discussion of products from the following manufacturers:
Abbott Laboratories (Androgel), Actient Pharmaceuticals (Striant), Auxilium Pharmaceuticals (Testim), Bartor Pharmacal (Testopel), Eli Lilly and Company (Axiron), Endo Pharmaceuticals (Fortesta), Pfizer (Depo-Testosterone), Savient Pharmaceuticals (Delatestryl), Watson Pharma (Androderm)

RECENT DRUG APPROVALS AND SIGNIFICANT EVENTS

New Drug Approvals

- Androderm 2 mg and 4 mg (testosterone) transdermal patches – October 2011
- Androgel 1.62% (testosterone) gel – April 2011
- Fortesta (testosterone) gel – December 2010
- Axiron (testosterone) topical solution – November 2010

FDA Alerts

- Testosterone gel products (AndroGel 1% and Testim 1%)
  [Posted 05/07/2009] FDA notified healthcare professionals that it will require two prescription topical testosterone gel products, AndroGel 1% and Testim 1%, to include a boxed warning on the products' labels after receiving reports of adverse effects in children who were inadvertently exposed to testosterone through contact with another person being treated with these products. Despite the currently labeled precautions, FDA has received reports of eight cases of secondary exposure to testosterone in children ranging in age from nine months to five years. Since that time, additional reports of secondary exposure have been received by the agency and are presently under review. Of the fully reviewed cases, adverse events reported in these children included inappropriate enlargement of the genitalia (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido and aggressive behavior. The gels are approved for use in men who either no longer produce testosterone or produce it in very low amounts. Both products are applied once daily, to the shoulders or upper arms. FDA has provided recommendations and precautions to minimize the potential for secondary exposure (1).

BACKGROUND

Testosterone therapy is approved by the U.S. Food and Drug Administration (FDA) for the treatment of delayed puberty in adolescent males, metastatic breast cancer in females, and male hypogonadism. Off

label use listed in the Centers for Medicare and Medicaid Services recognized compendia include improved cognitive function in hypogonadal and healthy older men, increased bone mineral density in hypogonadal and healthy men, increased weight gain in patients experiencing Acquired Immunodeficiency Syndrome (AIDS) wasting, and female to male transsexual/gender identity disorder (2).

Delayed puberty
Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses of testosterone may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An X-ray of the hand and wrist to determine bone age should be taken every 6 months to assess the effect of treatment on epiphyseal centers (3).

Metastatic Breast Cancer
Testosterone therapy may be used secondarily in women with advancing inoperable metastatic (skeletal) breast cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries through negative feedback on the hypothalamic pituitary axis suppressing the release of luteinizing hormone and follicle stimulating hormone from the anterior pituitary. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or antiestrogen therapy. This treatment has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field. Women with metastatic breast carcinoma must be followed closely because androgen therapy occasionally appears to accelerate the disease (3).

Primary and Secondary (Hypogonadotropic) Hypogonadism
The remainder of this therapeutic class review will focus on testosterone replacement agents used for the treatment of primary and secondary hypogonadism. The same principles apply to all individuals on testosterone replacement therapy (TRT).

Hypogonadism, also referred to as testosterone deficiency, affects approximately 30% of men ages 40 to 79 years (4). Studies have shown that 19% of men over 60 years have low testosterone, and the overall prevalence of hypogonadism is estimated to be approximately 39% in men aged 45 years or older. It has been estimated that only 5–35% of hypogonadal males actually receive treatment for their condition (4). The prevalence increases and is associated with age. As the US population ages, the likelihood of physicians encountering male patients with hypogonadism will increase. The number of individuals age 65 years and over is projected to rise from approximately 40 million (13.0%) in 2010 to approximately 60 million (17.9%) in 2025 (4).

Hypogonadism is defined as either primary or secondary. Primary hypogonadism affects the testicles directly resulting in low levels of serum testosterone and high LH and FSH levels. Secondary hypogonadism is caused by defects in hypothalamic-pituitary regulation resulting in insufficient

stimulation of the testes. It is associated with low to normal LH and FSH levels. A differentiating characteristic is that patients with secondary hypogonadism can have their fertility restored by suitable hormonal stimulation, whereas those with primary hypogonadism resulting from testicular failure cannot. Table 1 lists the causes of male hypogonadism (5).

Table 1. Causes of male hypogonadism

PRIMARY HYPOGONADISM	
Congenital anorchidism Cryptorchidism Mumps orchitis Genetic and developmental conditions: Klinefelter syndrome, androgen receptor and enzyme defects Sertoli cell only syndrome Radiation treatment / chemotherapy Testicular trauma Autoimmune syndromes (anti-Leydig cell disorders)	
SECONDARY HYPOGONADISM	
Genetic conditions: Kallmann's syndrome, Prader-Willi syndrome Pituitary tumors, granulomas, abscesses Hyperprolactinemia Cranial trauma Radiation treatment Various medications (corticosteroids, opioids)	Alcohol abuse Ageing Chronic infections (HIV) Hemochromatosis Systemic disease (liver failure, uremia, sickle-cell disease)

Symptoms of testosterone deficiency (TD) depend on the age of onset. When TD develops before the age of puberty, the manifestations are those of impaired or delayed puberty resulting in the lack of male secondary sex characteristics, such as:

- Small testes, phallus, and prostate
- Scant pubic and axillary hair
- Disproportionately long arms and legs (from delayed epiphyseal closure)
- Reduced male musculature
- Gynecomastia
- Persistently high-pitched voice

TD after the age of puberty results in a combination of symptoms that are difficult to discern as TD and are often attributed to aging. Table 2 lists the most common signs and symptoms of testosterone deficiency in adult males. Of these, the most common symptoms are sexual dysfunction and chronic fatigue (6) (7).

Table 2. Clinical manifestations of testosterone deficiency		
Physical	**Psychological**	**Sexual**
Decreased BMD Decreased muscle mass and strength Increased body fat or BMI Gynecomastia Anemia Frailty Fatigue	Depressed mood Diminished energy, sense of vitality, or well-being Impaired cognition and memory	Diminished libido Erectile dysfunction Difficulty achieving orgasm Decreased morning erections Decreased performance

RECOGNIZED TREATMENT GUIDELINE REVIEW

The overall clinical significance of TD, especially in younger male patients, is unclear. Various clinical studies have shown higher all-cause mortality, especially mortality due to cardiovascular disease (5). TD is also associated with an increased risk of obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome and hypertension (6). This relationship with an increase in cardiovascular risk factors, especially metabolic syndrome, is bidirectional and causality cannot be determined in either direction. It is not yet understood whether the low testosterone levels are a result of the disease or one of its causes. The Hypogonadism in Males study calculated odds ratios for some of comorbidities associated with TD (Table 3) (8). In a study of 858 veterans mortality rates over a mean of 4.3 years in patients with low, equivocal (equal number of low and normal), and low T levels was 20.1%, 24.6%, and 34.9%, respectively (9). A larger study of men aged 40-79 years with an average follow-up of seven years found that every 173 ng/dL increase in serum T was associated with a 21 % lower risk of all cause death. This was after excluding for deaths within the first 2 years and controlling for multiple other comorbidities and variables including age, body mass index, systolic blood pressure, cholesterol, cigarette smoking diabetes, alcohol intake, physical activity, social class, education, and sex hormone-binding globulin (10). The Rancho Bernardo study, with an average follow up of 11.8 years and up to 20 years total, also determined that serum testosterone levels were inversely related to the risk of death, including death from cardiovascular and respiratory causes (11).

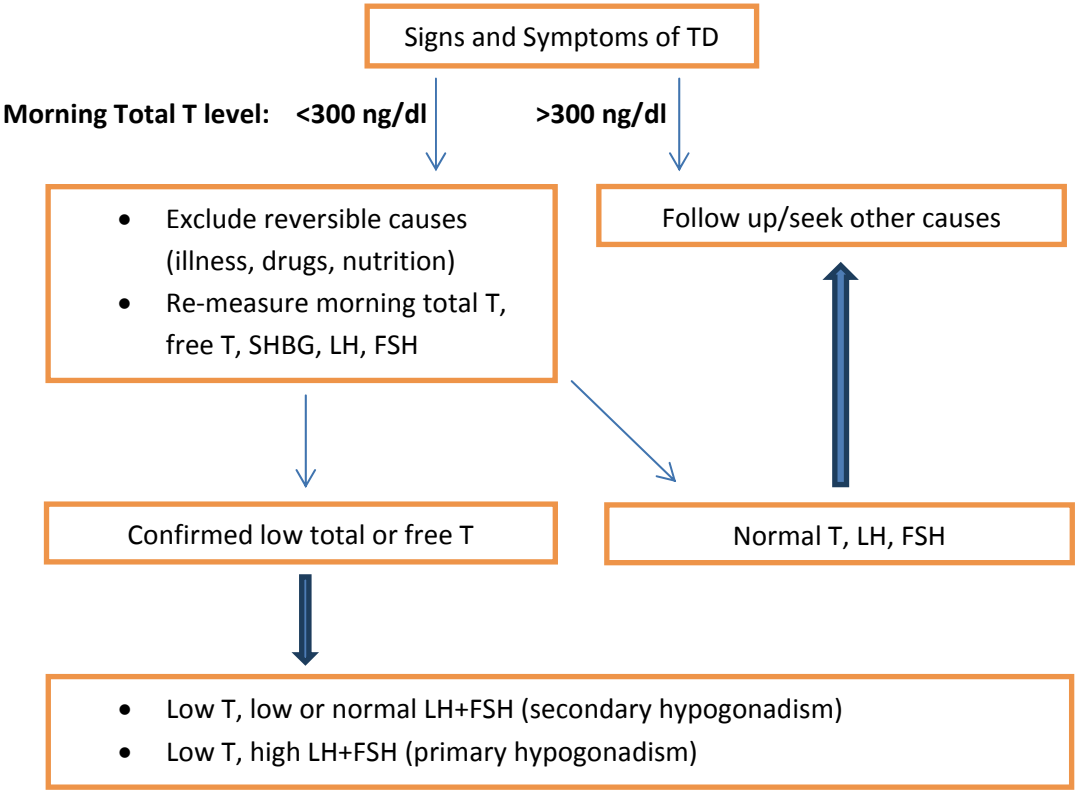
Table 3. Odds ratios for hypogonadism for various comorbidities	
Condition	**Odds Ratio**
Obesity	2.38
Diabetes	2.09
Hypertension	1.84
Hyperlipidemia	1.47
Osteoporosis	1.41
Asthma / chronic obstructive pulmonary disease	1.40

Diagnosis

Diagnosis of TD is based on clinical signs and symptoms consistent with low T, combined with low serum testosterone levels. The Massachusetts Male Ageing Study (MMAS) measured a combination of

testosterone levels and hypogonadal symptoms and found between 6% and 12% of men had symptomatic androgen deficiency (12). Half of the men in MMAS found to have symptomatic androgen deficiency at one stage had normal testosterone levels when retested at a second time. This is theorized to be responsible to natural variations in testosterone secretion and levels when signs and symptoms are present. As discussed below, a measurement of low testosterone in a patient should be reconfirmed at a later stage before considering treatment. Figure 1 shows an algorithm for the diagnosis of TD based on recommendations from The Endocrine Society (5).

Figure 1. Algorithm for the diagnosis of TD. FSH = follicle stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone-binding globulin; T = testosterone; TD = testosterone deficiency



The lower limit of normal total T differs depending on definitions provided by the different societies and their associated clinical practice guidelines. The Endocrine Society recommends 300 ng/dl (10.4 nmol/l) as a good level to consider as the lower limit of normal total testosterone (5). The AACE suggests 200 ng/dl (7), and the International Society of Andrology (ISA), International Society for the Study of Ageing Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), American Society of Andrology (ASA) recommendations suggest 230 ng/dl is a limit below which patients will usually benefit from testosterone replacement treatment (13). Total testosterone represents the total of free, sex hormone-binding globulin (SHBG) bound, and albumin-bound testosterone. Current recommendations emphasize the importance of confirming low T with two morning T levels. If the first level falls between 230 and 350 ng/dL, a questionable range according to current guidelines, then repeating the measurement of total T with SHBG may be helpful. This is because SHBG levels are easily

affected by many conditions, so total testosterone measurements can therefore be misleading indicators of hypogonadism (13). Two factors, aging and obesity are common in this population and can significantly affect SHGB levels (4). In patients other than young healthy males it is recommended to measure free testosterone in addition to total testosterone. The lower limit of the normal free testosterone range is approximately 5–9 ng/dL according to The Endocrine Society (5).

Treatment: Testosterone Replacement Therapy
Testosterone therapy can be initiated with any of the FDA approved agents. Consideration should be taken when evaluating patient preference, dosing schedule, formulation specific adverse reactions, differences in pharmacokinetics, and cost. According to The Endocrine Society recommendations, the goal of therapy should be to maintain testosterone levels between 350 to 750 ng/dL (5). Other guidelines have similar recommendations ranging from 280 to 1000 ng/dL (7) (13). For a cost comparison please refer to the MedImpact book of business drug utilization and cost tables below.

Intramuscular (IM) Injections (3) (14)
The testosterone esters, which include testosterone cypionate and testosterone enanthate, have been available as IM injections since the 1950's. These are available as generics and are usually the least costly of all testosterone formulations. The only caveat being they are IM injections and may require a provider visit for administration. They are available for self-administration by either the patient or a trained individual designated by the patient. They are supplied as 100 to 200 mg/ml concentrations with a typical dose of 100 to 200 mg every 1 to 2 weeks, respectively.

The injectable formulations initially cause an increase in serum testosterone to supraphysiological levels. Since they are dosed either once a week or once every two weeks, by the end of the dosing interval testosterone levels decline to pre-treatment levels and the patient may experience hypogonadal symptoms. Variations in symptomatic response or adverse effects of therapy have been observed later in the dosing interval accounting for changes in mood, sexual function and activity, and symptoms of fatigue correlating with the reduction in serum testosterone levels over time. Extreme variations in testosterone levels can be avoided by increasing the frequency of injections. Realistically, this is unfeasible given the frequent injections required of small doses.

Transdermal Patch (Androderm) (15) (4)
The testosterone transdermal patch, when applied nightly, mimics the diurnal circadian secretion of testosterone by a non-hypogonadal adult male. They are supplied in 2 and 4 mg per day systems applied to the skin of the back, abdomen, upper arms, or thighs. The Androderm 2.5 and 5 mg per day transdermal systems have been discontinued by the manufacturer with instructions to switch 2.5, 5, and 7.5 mg/day systems applied once daily to 2, 4, and 6 mg/day, respectively, applied once daily in the evening at the next scheduled dose. Testosterone levels should be checked in the morning with levels between 400 and 930 ng/dL requiring no dosage adjustment. The transdermal patch avoids the oscillations in serum testosterone levels observed with IM formulations and also offers an ease of application. Alternatively, if serum testosterone levels after initiating therapy are found to be subtherapeutic multiple patches may need to be applied nightly in order to achieve adequate therapy. In addition, skin irritation is common with the transdermal patch, with 23% of clinical trial participants

reporting an application site reaction. Mild skin irritation can be treated with over-the-counter topical hydrocortisone cream applied after system removal. Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the patch has been shown to reduce the incidence and severity of skin irritation.

Transdermal Gel (Androgel, Fortesta, Testim) (16) (17) (18) (19)
These are supplied as hydroalcoholic 1% and 1.62% gels in either a metered-dose pump or unit-dose packet. They are applied to intact skin of the upper arms and shoulders. Starting doses are 5 g for the 1% strength and 2.5 g for the 1.62% strength. Similar to the patch, the gel offers a dosage form free of serum testosterone level peaks and troughs experienced with each dose of the IM testosterone esters. Serum testosterone levels reach steady-state within 24 hours of application and remain in the normal range for the duration of the application. The gel offers the advantage of discreet dosing, with ease of application and improved skin tolerability over the patch, with approximately 5% of trial participants experiencing a reaction at the application site. The drawback to the gel formulation is the risk of transfer to a partner or child. Precautions such as hand washing after application, covering of the application site, and washing the application site when skin to skin contact is expected are recommended and can mitigate the potential for transfer. The 1.62% strength allows for a reduction in the total volume of gel applied, thereby reducing the opportunity for the patient to transfer active ingredient to his partner or child after skin contact.

Transdermal Solution (Axiron) (20)
Axiron is a testosterone solution, similar to the gel, applied to dry intact skin of the axilla, not to any other parts of the body including the abdomen or genitals. The starting dose is 60 mg of testosterone (1 pump actuation of 30 mg of testosterone to each axilla), applied once daily, at the same time each morning. Application site irritation is similar to the gel formulations with 7% and 8% of clinical trial subjects experiencing application site irritation at 120 and 180 days of therapy, respectively. Like the gel, application is easy and unnoticeable. Axiron also delivers physiologic circulating testosterone that approximates the normal concentration range seen in healthy men. The potential for secondary exposure still exists and precautions should be taken similar to the testosterone gels to prevent transfer to children and women.

Buccal Tablet (Striant) (21)
These are 30 mg controlled release muco-adhesive tablets applied twice daily to the area on your upper gum, just above either the left or right incisor. They release testosterone slowly, allowing for absorption through the gum and cheek surfaces. In this manner they bypass first-pass hepatic metabolism. The tablet must remain in the mouth for a full 12 h and two are needed for the 24 h dosing period. The incidence of adverse effects is low, although gum and buccal irritation were reported in 15% of study subjects during clinical trials. Alterations in taste were also reported in 6% of study participants. Other disadvantages are the tablet falling off prior to 8 to 12 hours of application or adhering to other parts of the mouth. The mucoadhesive dosage form can also get in the way of eating, drinking and brushing teeth.

Subcutaneous Implant (Testopel) (22) (4)
This is one of the earliest dosage forms and has been available since the 1940's. Currently they are provided in 75 mg pellets. The prescribing information recommends 150 mg to 450 mg (2 to 6 pellets) subcutaneously every 3 to 6 months. The testosterone pellets are usually implanted under the skin of the lower abdomen or are inserted into the gluteus muscle. Testosterone pellets currently are the only long-acting testosterone treatment approved for use in the United States. As a result of their long lasting effect and the inconvenience of removing them, it is best to use pellets in men for whom the beneficial effects and tolerance for testosterone replacement therapy have already been established. Inflammation and pain at the site of subcutaneous implantation of testosterone containing pellets, and rarely anaphylactoid reactions, have been reported. There have also been reports of spontaneous pellet extrusion requiring surgical reinsertion.

SAFETY CONSIDERATIONS

Contraindications
Testosterone therapy is contraindicated in men with breast cancer or known or suspected carcinoma of the prostate. Metastatic prostate cancers and breast cancer are hormone-dependent cancers that may be stimulated to grow during testosterone treatment therefore testosterone should not be administered to men with these cancers. Testosterone therapy is also contraindicated in women who are or plan to become pregnant due to the risk of virilization of the unborn fetus. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with testosterone gels and solutions, such as Androgel, Fortesta, Testim, and Axiron (16) (17) (19) (18) (3) (15) (20).

Warnings and Precautions
Secondary exposure to testosterone in children and women can occur with testosterone gel or solution use in men. Cases of secondary exposure resulting in virilization of children have been reported in post-marketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age (1).

There is little evidence to suggest testosterone therapy increases the risk of prostate cancer or will convert subclinical prostate cancer to detectable prostate cancer. In patients with signs or symptoms of prostate cancer or benign prostatic hyperplasia (BPH), the risk of developing active prostate cancer should be estimated, taking into consideration age, ethnicity, PSA, findings of digital rectal examination, family history, the use of 5-alpha reductase inhibitors, and biopsy results or history (5) (6) (4).

Additional warnings and precautions for the use of testosterone are suppression of spermatogenesis, hepatic disease, edema, gynecomastia, sleep apnea, and erythrocytosis. It is recommended that men with significant erythrocytosis (defined as a hematocrit greater than 54%), untreated obstructive sleep

apnea, or untreated severe congestive heart failure be treated for their comorbid condition prior to initiating testosterone therapy (5) (4) (16) (17) (19) (22) (18) (15) (14) (3).

Table 4, adapted from The Endocrine Society clinical guideline, summarizes potential adverse effects associated with testosterone therapy, including those that are specific to each dosage form (5).

Table 4. Warnings, precautions, and adverse effects associated with testosterone replacement therapy	
Contraindications	Breast Cancer
	Known or suspected prostate cancer
	Hypersensitivity to any of the ingredients in the formulation prescribed
Warnings and Precautions	BPH or increased risk of prostate cancer
	Risk of secondary exposure to gels and solutions
	Suppression of spermatogenesis
	Hepatic adverse effects
	Edema due to sodium and water retention. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease.
	Gynecomastia
	Sleep Apnea. The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.
	Erythrocytosis. Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Increase in red blood cell mass may increase the risk for a thromboembolic event.
Formulation Specific Adverse Effects	
Transdermal Patches	Application site reactions
IM Injections	Pain at injection site
	Fluctuation in mood and libido
	Excessive erythrocytosis, especially in older patients
Transdermal Gel	Risk of secondary exposure
Buccal Tablets	Gum irritation
	Alterations in taste
Pellet Implants	Risk of infection at incision site
	Early expulsion of pellets

Cardiovascular Risk of Testosterone Therapy

Data from a 2010 randomized placebo-controlled trial of testosterone replacement therapy in elderly frail men with limited mobility suggested potential improvements in muscle strength, body composition, and somatic and sexual symptom scores when testosterone levels were maintained in the physiological range. In addition no adverse cardiovascular events reported were attributed to testosterone therapy (23). The results of the 2010 Testosterone in Older Men with Mobility Limitations (TOM) trial showed different results, with an increase in cardiovascular events associated with testosterone therapy compared to placebo leading to study termination (24). Study limitations included a small sample size, and an elderly study population with multiple comorbidities. Mean age was 74 years and a large percentage of study participants in the TOM trial had subclinical cardiovascular diseases and a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity. Baseline characteristics were similar in the treatment versus the placebo arm except for greater statin and antihypertensive use in the testosterone group. The starting testosterone dose was also double the manufacturer and The Endocrine Society treatment guideline recommended starting dose for testosterone supplementation (24). Lastly, a meta-analysis, also published in 2010, comparing the risk of adverse events in adult men on testosterone therapy, found no additional risk in cardiovascular outcomes associated with testosterone therapy. Treatment was associated with a significant decrease in high-density lipoprotein cholesterol (-0.49 mg/dl; 95% CI, 0.85 to 0.13) (25).

Monitoring

Patients receiving testosterone replacement therapy should be evaluated three to six months after treatment initiation then annually to assess response to therapy defined as resolution of symptoms and serum testosterone levels in the normal to mid normal range. The patient should also be assessed for any adverse effects as a result of therapy. A mid normal range serum testosterone is defined as 400 to 700 ng/dl, and dosing adjustments should be made for patients who are supratherapeutic or subtherapeutic. Hematocrit levels should also be checked every 3 to 6 months then annually. It is recommended to stop therapy if the hematocrit is greater than 54%. Therapy can be resumed after the hematocrit has decreased to a safe level. For patients with a diagnosis of osteoporosis or low trauma fracture it is recommended to have a bone mineral density test 1 to 2 years after starting therapy. A urological consultation is only recommended in men with an increased risk of prostate cancer or a history of BPH or lower urinary tract symptoms (5) (4).

CONCLUSIONS

Testosterone replacement agents are indicated for the treatment of delayed puberty, breast cancer, and hypogonadism, with a majority of use in adult male patients being treated for primary or secondary hypogonadism. Testosterone deficiency is prevalent in older men and associated with type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome. Although testosterone therapy indirectly improves cardiovascular risk factors by improving body composition such as lowering percent body fat and increasing muscle mass, testosterone therapy should not be used to treat risk factors for cardiovascular disease. Diagnosis of testosterone deficiency should be accompanied with a total serum testosterone level below the lower limit of normal as defined by the lab specific reference range. The risks and benefits of testosterone therapy must be assessed with every patient. All testosterone replacement agents are equally effective and can be used to treat testosterone deficiency. The selection of one formulation over another should be based on patient and prescriber preference,

potential for adverse effects, and cost. Routine monitoring is required especially in patients at risk for breast and prostate cancer, and also to assess response to treatment. If there is no improvement of signs and symptoms, treatment should be discontinued and other causes investigated.

Cost

Drug	Dosage Form & Strength	Dosage
Androderm	2.5 mg Patch	5 mg daily
Androderm	5 mg Patch	5 mg daily
Androderm	2 mg Patch	2 mg daily
Androderm	4 mg Patch	4 mg daily
Androgel 1%	25 mg/2.5 g gel	50 mg daily
Androgel 1%	50 mg/5 g gel	50 mg daily
Androgel 1.62% gel pump	20.25 mg/1.25 g per actuation, gel	40.5 mg daily
Androgel 1% gel pump	12.5 mg/1.25 g per actuation gel	50 mg daily
Axiron	30 mg/actuation soln	60 mg daily
Fortesta	10 mg gel pump	40 mg daily
Striant	30 mg mucoadhesive	30 mg twice daily
Testim 1%	50 mg/5 g gel	50 mg daily
Testopel	75 mg pellets	150-450 mg every 3 to 6 months
Testosterone Cypionate	100 mg/ml IM injection	50-400 mg every 2 to 4 weeks
Testosterone Cypionate	200 mg/ml IM injection	50-400 mg every 2 to 4 weeks
Testosterone Enanthate	100 mg/ml IM injection	50-400 mg every 2 to 4 weeks

Indications

Drug	Delayed Puberty, Male	Hypogonadism	Metastatic BC	Cognitive fxn	Gender identity D/O	Osteoporosis, Male	Weight Gain (HIV)
Androderm (Patch)		X					√CMS
Androgel (Gel)		X				√CMS	
Testim (Gel)		X				√CMS	
Fortesta (Gel)		X				√CMS	
Axiron (Solution)		X					
Striant (Buccal)		X					
Testopel (SQ Implant)	X	X					
Testosterone Enanthate (IM)	X	X	X	√CMS	√CMS		√CMS
Testosterone Cypionate (IM)		X			√CMS		

X = FDA approved indication; √**CMS** = CMS compendia supported use

References

1. **FDA.** MedWatch. *www.fda.gov.* [Online] May 7, 2009. [Cited: December 13, 2011.] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm149346.htm.

2. **Thomson Reuters.** www.thomsonhc.com/micromedex2. *MICROMEDEX.* [Online] [Cited: 3 2012, January .] http://www.thomsonhc.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/4B4B71/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/EC821B/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/pf.HomePage.

3. **Endo Pharmaceuticals, Inc. .** *Delatestryl package insert.* Chadds Ford, PA : s.n., June, 2011.

4. *A practical guide to male hypogonadism in the primary care setting.* **Dandona P, Rosenberg MT.** 6, May 2010, The International Journal of Clinical Practice, Vol. 64, pp. 682-696.

5. *Testosterone therapy in adult men with androgen deficiency syndromes.* **The Endocrine Society.** 6, June 2010, The Journal of Clinical Endocrinology and Metabolism, Vol. 95, pp. 2536-2559.

6. *Testosterone Deficiency.* **Abdulmaged M, et.al.** 7, 2011, The American Journal of Medicine, Vol. 124, pp. 578-587.

7. *American Association of Clinical Endocrinologists Medical Guideline for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients.* **American Association of Clinical Endocrinologists.** 6, 2002, Endocrine Practice, Vol. 8, pp. 439-456.

8. *Prevalence of hypogonadism in males ages at least 45 years : the HIM study.* **Mulligan T, Frick MF, Zuraw QC, et al.** 2006, International Journal of Clinical Practice, Vol. 60, pp. 762-769.

9. *Low serum testosteorne and mortality in male veterans.* **Shores MM, Matsumoto AM, et al.** 2006, Archives of Internal Medicine, Vol. 166, pp. 1660-1665.

10. *Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prosepctive Population Study .* **Khaw KT, Dowsett M, Folker E, et al.** 2007, Circulation, Vol. 16, pp. 2694-2701.

11. *Low serum testosterone and mortality in older men.* **Laughlin GA, Barrett-Connor E, et al.** 2008, Journal of Clinical Endocrinology and Metabolism, Vol. 93, pp. 68-75.

12. *Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study.* **Araujo AB, O'Donnell AB, et al.** 2004, Journal of Clinical Endocrinology and Metabolism, Vol. 89, pp. 5920-5926.

13. *Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations.* 1, 2009, Journal of Andrology, Vol. 30, pp. 1-9.

14. **Pharmacia & Upjohn Company .** *Depo-Testosterone package insert.* New York, NY : s.n., September 2006.

15. **Watson Pharma, Inc.** *Androderm package insert.* Parsippany, NJ : s.n., October 2011.

16. **Abbott Laboratories.** *Androgel 1% package insert.* North Chicago, IL : s.n., November, 2011.

17. —. *Androgel 1.62% package insert.* North Chicago, IL : s.n., April, 2011.

18. **Endo Pharmaceuticals.** *Fortesta package insert.* Chadds Ford, PA : s.n., April, 2011.

19. **Auxilium Pharmaceuticals, Inc.** *Testim package insert. .* Malvern, PA : s.n., September 2009.

20. **Lilly USA, LLC.** *Axiron Package Insert.* Indianapolis, IN : s.n., July, 2011.

21. **Columbia Laboratories, Inc.** *Striant package insert. .* Livingston, NJ : s.n., February 2007.

22. **Bartor Pharmacal Co.; Inc.** *Testopel package insert.* Rye, NY : s.n., January 2009.

23. *Effects of testosterone on muscle strengh, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study.* **Srinivas-Shankar U, Roberts S, et al.** 2010, Journal of Clinical Endocrinology and Metabolism, Vol. 95, pp. 639-650.

24. *Adverse events associated with testosterone administration.* **Basaria S, Coviello AD, et al.** 2010, New England Journal of Medicine, Vol. 363, pp. 109-122.

25. *Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis.* **Fernandez-Balsells MM, Murad MH, et al.** 2010, Journal of Clinical Endocrinology and Metabolism, Vol. 95, pp. 2560-2575.